319:511-514 ("Heldin"). This rejection is respectfully traversed, as discussed below.

Applicants note with appreciation the withdrawal of the previous rejections under 35 USC §112, first and second paragraphs, as well as the previous rejections under 35 USC §102(a) and 35 USC §102(e).

New claims 55, 56 and 57 have been added which depend from claims 43, 44 and 45, respectively. The new claims recite that the pharmaceutically acceptable excipient is "suitable for topical administration." Support for the new claims can be found throughout the specification at, *inter alia*, page 13, lines 9-30. Thus, no new matter has been added to the application by way of the amendments.

Rejection Under 35 USC §102(b)

Claims 25-27 and 43-45 were rejected under 35 USC §102(b) as anticipated by Heldin et al., *Nature* (1986) 319:511-514 ("Heldin"). The Office maintains the previous rejection of claims 25-27, and further asserts, with respect to claims 43-45, that Heldin discloses the use of purified PDGF A-chain homodimer in cell culture medium in growth-promoting activity assays. The Action reasons that cell culture medium is a pharmaceutically acceptable excipient and, therefore, Heldin anticipates claims 43-45. However, applicants believe the present claims distinguish over Heldin.

In this regard, as previously explained, applicants' recombinant protein preparations are devoid of molecules present in cells that naturally produce the protein and, importantly, free of any viruses known to contaminate human cell lines. Thus, a recombinant protein

preparation both distinguishes from, and has significant advantages over, the prior art.

Applicants maintain their position that a purified protein from a human cellular source, such as a PDGF A-chain homodimer derived from a human osteosarcoma cell line, will necessarily contain human protein contaminants. As previously noted, conventional protein purification methods used to isolate PDGF from human cells would not result in a completely pure product but, rather, one which would inherently include at least small, perhaps undetectable by then available techniques, amounts of human proteins other than human PDGF A-chain homodimer. Therefore, applicants continue to assert that Heldin's preparation cannot be without other human proteins.

To evidence that such is the case, applicants are submitting the Declaration of Christer Betsholtz, Ph.D. ("the Declaration"). Dr. Betsholtz has over 15 years of experience working with the PDGF molecule. As stated in paragraph 5 of the Declaration, the product of each of the chromatographic columns used by Heldin to purify ODGF "would inherently include at least small amounts of human proteins other than human ODGF since the ODGF was isolated from human osteosarcoma cells." Moreover, Dr. Betsholtz states that the purification methods used by Heldin "cannot result in a protein product free of contaminating protein."

The Action argues that no bands other than PDGF A-chain homodimer were visible in silver-stained SDS polyacrylamide gels and no other amino acid sequence was obtained from the PDGF A-chain homodimer preparation. Despite these observations, Dr. Betsholtz notes in paragraph 5 of the Declaration "it is a virtual certainty that trace

amounts of human proteins were present in the ODGF preparations that were not detected by these methods."

Furthermore, the Action states that Heldin's ODGF "would be highly unlikely to be contaminated with virus." Office Action, page 4. However, as explained in paragraph 4 of the Declaration, the cell line from which ODGF was isolated was established from a human patient suffering from cancer. Although this cell line was propagated in culture, it is Dr. Betsholtz's belief "the cell line may well have contained pathogenic viruses from the patient." Additionally, since the cell line was of human origin, "it could easily become infected with human pathogenic viruses during propagation." The methods used by Heldin to purify ODGF "would not guarantee the elimination of human viruses" and hence "would not be appropriate for producing an ODGF compound to be used in pharmaceutical compositions since viral contaminants may be present. Accordingly, there would be a high risk associated with using ODGF purified as described in Heldin, in compositions for treating patients." (See, paragraph 4 of the Declaration).

As explained in paragraph 6 of the Declaration, recombinant methods of producing PDGF A-chain homodimer, on the other hand, "result in a preparation free of other human proteins and devoid of contaminating human viruses" since the only human structural gene present in the recombinant plasmids is the gene encoding human PDGF. Such purity cannot be achieved absent the gene encoding PDGF. Heldin does not describe the gene or recombinant methods for producing PDGF A-chain.

In light of the above discussion, applicants submit that the Heldin product, unlike the claimed preparation, would inherently include at least residual amounts of other

human proteins, possibly viruses, and would not be useful in therapeutic compositions. Therefore, applicants respectfully request withdrawal of the § 102(b) rejection.

New claims 55-57 are also free of the art. These claims relate to protein preparations comprising PDGF A-chain homodimers in combination with a pharmaceutical excipient that is "suitable for topical administration." Heldin does not disclose or suggest pharmaceutical compositions, let alone those suitable for topical administration. Accordingly, these claims are also patentable over Heldin.

Conclusion

Applicants respectfully submit that the claims define an invention which is novel and nonobvious over the art. Accordingly, allowance is believed to be in order and an early notification to that effect would be appreciated.

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